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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/701,013	01/12/2001	Masaaki Terada	0020-4769P	4777

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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	10

DATE MAILED: 10/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No	Applicant(s)
09/701,013	Terada et al.
Examiner	**Art Unit**
Shin-Lin Chen	1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *Aug 28, 2002*

2a) ☐ This action is **FINAL.** 2b) X This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) X Claim(s) *1-29* is/are pending in the applica

4a) Of the above, claim(s) *18, 19, 28, and 29* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) X Claim(s) *1-17 and 20-27* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) X Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) X All b) ☐ Some* c) ☐ None of:

1. X Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) X Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) X Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other

DETAILED ACTION

1. Applicant's election with traverse of group I, claims 1-17 and 20-27, in Paper No. 9 is acknowledged. The traversal is on the ground(s) that the election is for the purpose of examination of the present application. This is not found persuasive because of the reasons of record.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 18, 19, 28 and 29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-17 and 20-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "and/or" in claim 1 is vague and renders the claim indefinite. It is unclear what is intended to be claimed. Changing the term "and/or" to "or..., or both" would be remedial. Claims 2-17 depend on claim 1 but fails to clarify the indefiniteness.

The phrase "a substance accelerating an introduction of the gene into a cell" in claims 9 and 22 is vague and renders the claims indefinite. It is unclear as to the metes and bounds of what would be considered "a substance accelerating an introduction of the gene into a cell"? The specification only provides a few examples, such as cationic lipid, but fails to specifically define the phrase.

The phrase "at least one amino acid, and a collagen, or a gelatin" in claim 20 is vague and renders the claim indefinite. It is unclear what is intended to be claimed: at least one amino acid and a collagen, or at least one amino acid or a gelatin, or at least one amino acid and a gelatin, or at least one amino acid and a collagen and a gelatin. Claims 21-27 depend on claim 20 but fail to clarify the indefiniteness.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-4, 7-13 and 15-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Szoka et al., 1996 (WO 96/40265).

Claims 1-4, 7-13 and 15-17 are directed to a stable gene formulation which comprises a desired gene or a vector incorporated with a desired gene and at least one saccharide, such as

glucose, fructose, sucrose, trehalose, or mannitol, and or at least one non-hydrophobic amino acid, such as glutamic acid or aspartic acid, and/or at least one organic acid having two or more carboxyl groups except amino acids, such as citric acid or tartaric acid. Claim 8 specifies the formulation is a solution, a gel or a suspension, and the saccharide or the non-hydrophobic amino acids is about 1 w/v% or more. Claims 9 and 10 specify the formation further comprises a substance accelerating an introduction of the gene into a cell, such as a cationic lipid. Claims 11-13 specify the formulation further comprises a pharmaceutically acceptable additive that is biocompatible. Claims 15-17 specify the gene formulation is in a dried state and is dried by lyophilization.

Szoka teaches polynucleotide complexes stabilized by adding a cryoprotectant compound, such as carbohydrate including lactose at a concentration of about 1.25% to 10% w/v, sucrose, glucose, mannitol, sorbitol, trehalose. The polynucleotide complexes could be plasmid DNA, polynucleoteide associated with a cationic lipid, or a polynucleotide associated with a liposome or lipidic particle. Szoka also teaches further adding amino acid, such as betaines prolines, polylysine, to stabilize the polynucleotide complexes (e.g. abstract, p. 2, 22). Szoka teaches lyophilization of the polynucleotide complexes and the lyophilized formulation may be stored for extended period of time and then rehydrate prior to use for gene delivery (e.g. abstract, p. 1, 24). The carbohydrate and amino acid are considered a pharmaceutically acceptable additive that is biocompatible. Thus, claims 1-4, 7-13 and 15-17 are anticipated by Szoka.

7. Claims 1-4, 8, 11-13 and 15-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Kuma et al., 1996 (WO 96/29096).

Claims 1-4, 8, 11-13 and 15-17 are directed to a stable gene formulation which comprises a desired gene or a vector incorporated with a desired gene and at least one saccharide, such as glucose, fructose, sucrose, trehalose, or mannitol, and/or at least one non-hydrophobic amino acid, such as glutamic acid or aspartic acid, and/or at least one organic acid having two or more carboxyl groups except amino acids, such as citric acid or tartaric acid. Claim 8 specifies the formulation is a solution, a gel or a suspension, and the saccharide or the non-hydrophobic amino acids is about 1 w/v% or more. Claims 11-13 specify the formulation further comprises a pharmaceutically acceptable additive that is biocompatible. Claims 15-17 specify the gene formulation is in a dried state, and is dried by lyophilization.

Kuma teaches generation of gene transfer preparations comprising the addition of one or more additives including arginine, glutamic acid (or its sodium salt), serine, glucose, inositol, lactose, mannitol, sorbitol, and trehalose, to recombinant virus vectors, such as adenovirus vector, and lyophilization. Kuma teaches lyophilization method was developed to maintain gene transfer efficiency and the additives are low molecular weight substances that are used as medicinal additives (e.g. p. 7, 8). Kuma further teaches the weight ratio of each additives, such as amino acids and sugars with respect to vector solution is about 1 to 10% (e.g. p. 9). The sugars and amino acids are considered a pharmaceutically acceptable additive that is biocompatible. Thus, claims 1-4, 8, 11-13 and 15-17 are anticipated by Kuma.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1, 5, 6, 11, 12, 14 and 20-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Szoka et al., 1996 (WO 96/40265) in view of Fujioka et al., 1993 (US Patent No. 5,236,704).

Claims 1, 5, 6, 11, 12, 14 and 20-27 are directed to a stable gene formulation which comprises a desired gene or a vector incorporated with a desired gene and at least one saccharide, such as glucose, fructose, sucrose, trehalose, or mannitol, and/or at least one non-hydrophobic amino acid, such as glutamic acid or aspartic acid, and/or at least one organic acid having two or more carboxyl groups except amino acids, such as citric acid or tartaric acid. Claims 5 and 6

specify the organic acid has two or three carboxyl groups is citric acid or tartaric acid. Claim 14 specifies the biocompatible material is a collagen or a gelatin or a mixture thereof. Claims 20-27 specify the gene formulation comprises a desired gene or a vector, at least one amino acid, and a collagen or a gelatin.

Szoka teaches polynucleotide complexes stabilized by adding a cryoprotectant compound, such as carbohydrate including lactose at a concentration of about 1.25% to 10% w/v, sucrose, glucose, mannitol, sorbitol, trehalose. The polynucleotide complexes could be plasmid DNA, polynucleoteide associated with a cationic lipid, or a polynucleotide associated with a liposome or lipidic particle. Szoka also teaches further adding amino acid, such as betaines prolines, polylysine, to stabilize the polynucleotide complexes (e.g. abstract, p. 2, 22). Szoka teaches lyophilization of the polynucleotide complexes and the lyophilized formulation may be stored for extended period of time and then rehydrate prior to use for gene delivery (e.g. abstract, p. 1, 24).

Szoka does not teaches using aspartic acid, citric acid, or collagen or gelatin for gene formulation.

Fujioka teaches preparation of a controlled release formulation by lyophilizing a mixture of an active ingredient such as protein or peptide, a collagen and an organic acid compound having one or more carboxylic groups, such as citric acid and tartaric acid, as an additive, pulverizing the resulting solid product, and compression-molding the pulverized product in a template or charging the above-mentioned mixture in a template and condensing or drying the mixture, so as to obtain the formulation in a solid form, whereby any formulation, having a

desired size and shape suitable for a particular administration route and a particular position to be applied can be obtained (e.g. column 1, 2). Fujioka teaches sustained release formulations, which release an active ingredient over a long period of time, are useful for the increase of therapeutical effects due to prolonged retention of an active ingredient over effective level in the blood, the decrease of side-effects by reducing the maximal blood level of the active ingredient, simplification of administration methods and a reduction in a patient's level of pain due to a decrease of administration frequency (e.g. column 1).

It would have been obvious for one of ordinary skill at the time of the invention to use a collagen, a citric acid, or a tartaric acid for the preparation of a stable gene formulation because Fujioka teaches preparation of a controlled release formulation comprising an active ingredient, a collagen and a citric acid or tartaric acid, and said formulation can release the active ingredient over a long period of time for increased therapeutic effects of the active ingredient.

One having ordinary skill at the time the invention was made would have been motivated to do so in order to generate a stable polynucleotide complex for gene transfer in gene therapy as taught by Szoka or to produce sustained release formulations which release an active ingredient over a long period of time and are useful for the increase of therapeutical effects due to prolonged retention of an active ingredient over effective level in the blood, the decrease of side-effects by reducing the maximal blood level of the active ingredient, simplification of administration methods and a reduction in a patient's level of pain due to a decrease of administration frequency as taught by Fujioka with reasonable expectation of success.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Scott Priebe can be reached on (703) 308-7310. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.